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CHAPTER 9

OCCUPATIONAL EXPOSURES TO PETROCHEMICALS, AROMATIC AMINES, AND PESTICIDES

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Introduction

Workers employed in industries that produce or use petrochemicals, aromatic amines, and pesticides can be exposed to chemicals that threaten their health. Substantial proportions of these workers smoke tobacco. It is possible that the hazards of smoking and occupation have independent damaging effects on health, but it is also possible that the two exposures act synergistically. It is the purpose of this chapter to review the available evidence bearing on the hazards of working in industries where petrochemicals, aromatic amines, and pesticides are produced or utilized, and to explore the likelihood that smoking and chemical exposures interact to enhance the risk of various cancers and chronic obstructive lung disease. Unfortunately, there are very limited data on such potential interactions.

Petrochemical, Aromatic Amine, and Pesticide Workplace Exposures

The word "petrochemical" means any substance derived from petroleum or natural gas. By this definition, petrochemicals are pervasive in modern industry and agriculture, and worker exposure might logically include almost the entire workforce. Historically, however, concern about adverse effects on human health has focused mainly on industries where petroleum is separated into its many valuable components (refineries) or where the various products of that separation are used in such a way that workers are substantially exposed (manufacture of rubber and processing of leather, for example). Workers exposed to the products of inefficient hydrocarbon combustion (vehicle exhaust, coke production) are also objects of concern because they inhale unburned hydrocarbons and also the many reactive substances generated by pyrolysis.

A number of aromatic amines, such as betanaphthylamine and benzidine, are used in the manufacture of dyes for the textile and garment industries. Industrial exposure to some of these chemicals has been reduced because of the known carcinogenicity of betanaphthylamine and similar compounds. However, naphthylamines are sometimes used as antioxidants in the manufacture of rubber products, and significant numbers of workers are still exposed to benzidine, 4-aminobiphenyl, and other hazardous aromatic amine products. The groups of interest with regard to exposure are, therefore, rubber workers and people employed in the manufacture of aromatic amine dyes.

Workers exposed to pesticides include manufacturers, formulators, custom applicators, and end-users, principally farmers. Farming, as an occupational category, has been included in some epidemiologic studies. Degrees of pesticide exposure on the part of farmers vary enormously both qualitatively and quantitatively; therefore, the

assumption that the health status of farmers is a reflection of pesticide toxicity is, at best, dubious. This chapter focuses on the few studies of the health status of workers engaged in pesticide manufacture, formulation, or application.

Prevalence of Smoking in the Petrochemical, Aromatic Amine, and Pesticide Industries

Information on smoking habits has been very limited in occupational epidemiologic studies; there are no published reports that specifically describe the smoking habits of workers in the petrochemical, aromatic amine, and pesticide industries. A number of surveys have demonstrated the tremendous variability in smoking prevalence between occupational groups. The variation in smoking prevalence between occupational groups, discussed in chapter 2 in this Report, indicates that operatives and laborers have a higher prevalence of smoking and earlier ages of initiation.

Because levels of exposure to hazardous and potentially hazardous substances in the workplace are also greater in operatives and laborers, smoking can potentially confound attempts to relate workplace exposures to the development of certain diseases known to be related to cigarette smoking, such as lung and bladder cancer and chronic obstructive lung disease. The independent contributions of occupation and smoking to disease risk cannot be determined, nor can interactions be evaluated, without adequate measures of both exposures. Assumptions of equal smoking exposure within and between occupational cohorts are often tenuous. Few of the studies reviewed in this chapter measured occupational or tobacco exposure adequately.

Interactions of Workplace Exposure and Cigarette Smoking

A synergistic effect of two factors is one that exceeds the expected effects of the two factors acting additively. Reif (1984) has defined synergy quantitatively and unambiguously. Essentially, if the risk ratio for workers in a given occupational setting significantly exceeds the expected additive effects of two exposures acting separately, potentiation, or synergy, of the two factors is inferred. When the combined action equals the sum of the effects of the two agents working independently, the factors are additive. Similarly, if two factors work independently, but their dual effect is less than the sum of their independent effects, antagonism exists. Weiss (1980) reported that the risk of developing lung cancer after exposure to chloromethyl ethers (CME) was greater in nonsmokers and ex-smokers than in current smokers. This example of possible antagonism leads to speculation that the excess mucus that blankets the airways of smokers might diminish the carcinogenic effect of CME.

This may result because chloromethyl ethers are direct-acting carcinogens that hydrolyze in water.

To the extent possible, interactions between workplace exposure and cigarette smoking are discussed in terms of Reif's definitions.

Studies of Workers Exposed to Petrochemicals

Refinery, Coke Oven, and Gas Workers

The Bureau of Labor Statistics (US DOL 1984) reported that 83,200 workers were employed in petroleum refining in September 1984. These workers are exposed in varying degrees to crude petroleum and to various fractions produced in the refining process, including polycyclic aromatic hydrocarbons (PAH). Many of these substances have been shown to produce lung and kidney cancer in animals (IARC 1972).

Because of exposure to known carcinogens, a number of cohorts of refinery workers have been investigated. The results of these cohort mortality studies, summarized in Table 1, were not consistent regarding cancer risk, but were consistent in their lack of well-defined chemical exposures and the absence of information on smoking habits of individuals within the cohort. Some of these investigations suggested an increased risk of death for specific cancer types; others suggested a decreased risk.

Hanis and colleagues (1979) showed statistically significant increases in risk of death due to esophageal and stomach cancer combined and due to lung cancer. Combined mortality due to bladder and kidney cancer was also slightly greater than expected. Smoking could not be ruled out as a contributor to the increased risk in this group of refinery workers.

Thomas and colleagues (1982) observed increased proportionate mortality ratios for stomach and pancreatic cancer in their study of 2,500 refinery workers. Risks of death due to leukemia, prostatic cancer, brain neoplasia, and skin cancer also appeared to be elevated. The role that smoking might play in relation to the findings for stomach and pancreatic cancer was not discussed.

Hanis and colleagues (1982) demonstrated elevated risks of death due to pancreatic and kidney cancer in a cohort of refinery and chemical workers. Pancreatic and kidney cancer mortality was greater than expected by approximately 50 percent, but these elevations in observed deaths were not statistically significant. Although smoking information was not available for the entire cohort, 17 of the 24 pancreatic cancer deaths occurred in men who smoked (15 smoked cigarettes, 2 smoked cigars). Wen and colleagues (1983) also showed a slight, but nonsignificant, increase in pancreatic cancer in a cohort of refinery workers.

TABLE 1.—Epidemiologic studies of mortality among petrochemical industry workers and workers in related industries

Study	Type of population	Study design	Major findings
Hanis et al. (1979)	15,032 male petrochemical workers	Historical prospective mortality	Compared with nonexposed workers, men working in refineries had a relative risk of 3.25*, 1.89*, and 1.08 for dying of esophagus/stomach, lung, and bladder/kidney cancer, respectively ¹
Theriault and Goulet (1979)	1,205 male refinery workers	Historical prospective mortality	Three primary brain cancer deaths in this small cohort, less than one expected; fewer than expected lung cancer and respiratory disease deaths ¹
Rushton and Alderson (1981)	34,708 male petrochemical workers	Historical prospective mortality	Fewer than expected deaths due to lung cancer (SMR 0.78*), bladder cancer (SMR 0.77), and bronchitis (SMR 0.64*) ¹
Thomas et al. (1982)	2,509 oil refinery workers	Proportionate mortality	Proportionate mortality ratios (PMRs) 1.42* for pancreatic cancer, 1.14 for lung cancer, and 0.57 for respiratory disease, compared with U.S. men; PMRs elevated for stomach (1.52), prostate (1.38), skin (1.81), and lymphatic cancers (1.61) and leukemia (1.83) ¹
Hanis et al. (1982)	8,666 refinery and chemical plant workers	Historical prospective mortality	SMRs 0.92, 0.99, 1.53, 1.55 for death due to lung, pancreatic, bladder, and kidney cancer, respectively; medical records inadequate to control for smoking; of deaths due to pancreatic cancer, 71 percent (17/24) were in men with a history of tobacco smoking ²
Waxweiler et al. (1983)	7,595 petrochemical plant men	Historical prospective mortality	SMR 1.98 for mortality due to "total brain tumors"; SMR 0.78 for lung cancer and 0.64 for bladder cancer in hourly petrochemical workers; SMR 0.57* for nonmalignant respiratory disease deaths in white hourly workers ¹

TABLE 1.—Continued

Study	Type of population	Study design	Major findings
Austin and Schnatter (1983)	6,588 white male petrochemical workers	Historical prospective mortality	Essentially same cohort as Waxweiler et al. (1983); similar results ¹
Wen et al. (1983)	16,888 refinery workers	Historical prospective mortality	Fewer than expected deaths due to lung cancer (SMR 0.99), bladder cancer (SMR 0.46*), and nonmalignant respiratory diseases (SMR 0.68*); SMR 1.09 for cancer of pancreas; SMR 2.28* for bone cancer ¹
McCraw et al. (1985)	3,976 refinery workers	Historical prospective mortality	Fewer than expected deaths due to all cancers (SMR 0.91) and all respiratory tract diseases (SMR 0.44*); SMR 2.13* for leukemia ¹
Hanis et al. (1985a, b)	21,698 petrochemical workers	Historical prospective mortality	Small but significant increases in all cause and circulatory disease mortality in workers exposed to petrochemicals, differences not explained by smoking; small, statistically insignificant increases in all malignancy deaths and prostate and lung cancer deaths; compared with U.S. mortality rates, no significant increase in mortality for any cause in this cohort ¹
Redmond et al. (1972)	3,530 coke oven workers, subgroup of 59,000 steelworkers	Historical prospective mortality	Male coke oven workers had relative risks of 2.85* and 2.05* for dying of lung cancer and bladder cancer, respectively; relative risk 1.11 for other respiratory diseases ¹
Doll et al. (1972)	3,028 gas workers	Historical prospective mortality	Compared with unexposed workers, coal carbonization process workers had a relative risk of 2.40*, 2.35*, and 1.83* for dying of lung cancer, bladder cancer, and bronchitis, respectively ¹

*SCM significantly different from 1.00 at $p < .05$.

¹ Smoking history not considered.

* Smoking history considered.

Hanis and colleagues (1985a) expanded their previous work to include current employees and retirees of two additional U.S. refineries and chemical plants. They analyzed 3,198 deaths from 1970 through 1977 in an exposed population of 21,698 workers; standardized mortality ratios (SMRs) were calculated, using for comparison U.S. population mortality rates specific to age, sex, race, calendar year, and cause. Ninety-one percent of deaths in the refinery and chemical workers occurred among retirees. Although this study identified some causes of death that appeared to be either unusually frequent or infrequent in one or another of the three chemical plants studied, no statistically significant excesses or deficits of cause-specific mortalities were found for the cohort as a whole, relative to the general U.S. population. Specifically, neither brain tumors nor gastrointestinal cancers nor lymphopoietic malignancies were found to be unusually common in the full worker cohort, as previous studies of chemical plant workers had suggested. At one of the three plants, deaths caused by malignant neoplasms in general and by digestive organ cancers in particular were significantly in excess, but this result was counterbalanced by the unusually low mortality experience from these causes at the other two plants. The authors were impressed that certain subgroups of digestive and urinary organ cancers were increased. They speculate that smoking could have played a significant role in these findings.

In a second report on the same cohort, Hanis and colleagues (1985b) used direct standardization of mortality rates. This report categorized workers into nine occupational groups, of which five had "potential exposure" to petrochemicals in their work (process operators, mechanical workers, laborers, service workers, and laboratory technicians and field workers), and four had "no exposure" (officials and managers, professionals, technicians, and office and clerical workers), and compared mortality experience between these groupings. Comparisons used age, sex, race, and calendar-year adjusted rates. In the aggregate, all-cause mortality was higher for the potentially exposed workers (236.1 deaths/10,000/year) than for the nonexposed workers (189.1 deaths/10,000/year). This increase resulted from more circulatory system deaths (145.6 deaths/10,000/year versus 106.6 deaths/10,000/year) and malignant neoplasms (49.8 deaths/10,000/year versus 41.0 deaths/10,000/year) among the potentially exposed workers. The mortality rate for respiratory system diseases excluding lung cancer was lower for the potentially exposed workers (10.8 deaths/10,000/year versus 14.7 deaths/10,000/year). Smoking histories (ever smoked or never smoked) were available for 70 percent of the cohort. As a group, workers who had ever smoked had significantly elevated mortality rate ratios (relative risks) for all causes (1.9), all malignant neo-

plasmas (2.3), circulatory diseases (1.7), respiratory diseases (3.5), and diseases of the digestive system (2.2).

Among workers who had ever smoked, all-cause mortality and diseases of the circulatory system were increased in the subgroup of potentially exposed workers compared with the nonexposed workers (risk ratios 1.2 and 1.4, respectively). Rates for the potentially exposed groups who had never smoked were not elevated compared with the rates for the nonexposed who had never smoked. The number of deaths in these groups was small, so power for these comparisons is low. The analysis did not specifically test for an interaction between smoking and petrochemical exposure. Additional followup of this particular cohort may permit a more powerful analysis, including examination of the interaction of smoking and petrochemical exposure for specific cancer sites.

Certain epidemiologic studies have been directed at the hazards of specific tasks performed in the course of petroleum refining. The refining of lubrication oils involves exposure to unique solvents (benzene, hexane, methylethylketone, xylene, and toluene) and to the oils themselves, which have some carcinogenic potential. A recent study (Wen et al. 1985) focused on mortality among 1,008 male refinery workers engaged in the lubricating-dewaxing process at any time between 1935 and 1978; 210 observed deaths were analyzed by cause. Standardized mortality ratios were calculated, using for comparison rates specific for age, sex, race, and cause, based on the U.S. population at 5-year intervals from 1935 to 1975. Recently measured air concentrations of solvents were far below regulatory workplace standards. The standardized mortality ratio for all causes was 0.70 (significantly less than 1.0, $p=0.01$) and for malignant disease, 0.86 (not significantly different from 1.0). Of the site-specific cancer mortality ratios, only that for bone cancer was significantly elevated (SMR 10.3), but the elevation was based on only three cases, and subsequent investigation showed that only one of these was truly a mesenchymal tumor of bone origin. The other two represented metastatic cancers, one from a lung tumor and the other from a glial (brain) malignancy. Eight prostate cancer deaths were identified; the corresponding SMR of 1.82 was not significant. No deaths from cancer of the mouth or pharynx were observed, thus failing to confirm a previously reported association of these cancers with lubricating oil refining. No significant excess of leukemia deaths was found (SMR 1.67). No data on smoking habits were collected.

The other studies of refinery workers summarized in Table 1 showed an average or a decreased risk for lung and bladder cancer. Most showed a decreased risk for nonmalignant respiratory disease deaths, leading one group of researchers (Waxweiler et al. 1983) to speculate that strict enforcement of antismoking policies might be

responsible for the reduced risk of smoking-related diseases in refinery workers.

Cohort mortality studies in industries with similar environmental exposures are also described in Table 1. Redmond and colleagues (1972) described the increased risk of lung cancer and bladder cancer mortality in coke oven workers. The risk appears to result from exposure to PAH emitted in the exhaust created during the coking process. Unfortunately, smoking information was not collected in this classic study.

Doll and colleagues (1972) showed comparable results in their cohort study of gas workers. Coal carbonization workers who are exposed to PAH emitted by retort ovens had significant increases in mortality resulting from lung cancer, bladder cancer, and bronchitis. Smoking histories on a 10 percent random sample in this cohort showed that the smoking habits of gas workers in the retort houses did not differ from the habits of other gas workers. The authors concluded, therefore, that differences in smoking prevalence did not explain the mortality excess experienced by gas workers in retort houses. They commented that the sample size was too small to tell whether there was any interaction between smoking habits and the occupational hazard.

Rubber Workers

Workers engaged in the manufacture of rubber products have long been of concern to occupational health professionals because their work environments are commonly contaminated with dusts and the fumes of hundreds of industrial chemicals, including hydrocarbon solvents. The carcinogenic potential of a number of materials used in rubber manufacture—benzene, betanaphthylamine, and other amine and nitroso derivatives of hydrocarbons—is well documented in man, laboratory animals, or both. Worker exposure to some of the most likely carcinogens has been described (Mancuso and Brennan 1970; Monson and Fine 1978). In addition, exposure to talc, carbon black, and the dust from the milling and grinding processes represents a continuing hazard to the respiratory tract.

The feedstocks and solvents used in this industry are chemically diverse, and the mix of chemical exposures changes from one year to the next. Worker exposures are so different from one plant to another and from one time to another that it is questionable whether rubber manufacturing should be considered an "industry." Divergent findings from the many studies since Case and colleagues (1954) first attributed an excess of bladder cancer in rubber workers to their occupational exposure may well result from the diversity and evolution of pollutants in this unique work environment.

Production workers employed in manufacture, fabrication, and reclamation of rubber in September 1984 totaled 188,000 (US DOL

1984). There are no current estimates of the frequency or intensity of smoking in this specific segment of the workforce. Because of smoking restrictions at some worksites where explosion hazards exist, smoking may not be quite as pervasive among rubber workers as it is in other blue-collar populations who work where similar restrictions are not in effect.

Epidemiologic studies aimed at determining the risk of cancer attributable to employment in the rubber industry are summarized in Table 2. All of these studies are surveys of mortality experience over the last several decades. All but two were of the historical prospective design. In none was smoking taken into consideration as a factor contributing to cancer mortality. Direct information regarding the smoking habits of decedents was probably difficult, or impossible, to obtain. Also, with the exception of bladder cancer, the forms of malignancy most often identified as possibly excessive (brain, hematopoietic, lymphatic) are not commonly regarded as smoking-related cancers.

An early analysis of proportionate mortality in Akron, Ohio, rubber workers suggested excess rates of cancer affecting the respiratory, genitourinary, and central nervous systems (Mancuso et al. 1968). A subsequent historical prospective study (McMichael et al. 1974) analyzed 1,783 deaths by cause in a cohort of 6,678 male workers employed from January 1964 and compared cause-specific SMRs with rates based on the U.S. male population and on previously published rates for steelworkers. Elevated ratios suggested excess risks of malignant disease of the stomach, prostate, and lymphatic and hematopoietic systems. There was no indication of excess risk of cancer of the lung or bladder at one Akron plant, and only slight risk elevations at five other plants. No attempt was made to assess the impact of smoking. A followup study (McMichael et al. 1975) tended to associate leukemia deaths with job assignments involving solvent exposure.

In a prospective mortality study of rubber workers, Fox and colleagues (1974) demonstrated an increased risk of mortality due to all cancers combined and to bladder cancer specifically. In subsamples of this cohort, specifically workers in the tire sector and the hose rubber sector, significant increases in lung cancer mortality were observed. These sectors of the workforce had known exposures to asbestos. Smoking histories were not available in this study, although deaths due to bronchitis and emphysema were fewer than expected in tire workers.

A study of mortality and morbidity among Akron rubber workers included a cohort of 13,570 workers (Monson and Nakano 1976; Monson and Fine 1978). Information was assembled from death certificates, and incidence data were also collected from local hospital tumor registries. Comparisons were made between the

TABLE 2.—Epidemiologic studies of mortality among rubber workers

Study	Type of population	Study design	Controls	Disease status studied	Major findings
Mancuso et al. (1968)	1,877 rubber workers; 463 deaths	Historical prospective mortality	Office workers in rubber industry	All causes	Apparent excess mortalities from various malignancies among "nonoffice" workers, including cancers of the gastrointestinal tract, lung, and hematopoietic tissues; mortality from nonmalignant diseases of the circulatory and respiratory systems also apparently elevated; not tested statistically
Mancuso and Brennan (1970)	1,877 rubber workers	Historical prospective mortality	Office workers in rubber industry	Cancer of gallbladder, ducts, salivary glands	Apparent excess mortalities in particular plants and jobs from cancer of the gallbladder, bile ducts, and salivary glands; not tested statistically
Fox et al. (1974)	40,867 cablemakers	Historical prospective mortality	U.K. male population	All diseases	Elevated SMR for all neoplasms and bladder cancer mortality; greater than expected lung cancer mortality in tire makers and hose/rubber sector; fewer than expected deaths from bronchitis
McMichael et al. (1974)	6,678 male rubber workers	Historical prospective mortality	U.S. male population	All diseases	Elevated SMRs for neoplasms of gastrointestinal tract and lymphatic and hematopoietic systems; no excess of lung or bladder cancer or chronic pulmonary disease
McMichael et al. (1975)	6,678 male rubber workers; 8 leukemia deaths	Case-control	Other deceased rubber workers (matched)	Leukemia	Significant excess of mortality from lymphatic leukemia associated with past exposure to solvents

TABLE 2.—Continued

Study	Type of population	Study design	Controls	Disease status studied	Major findings
Monson and Nakano (1976)	13,571 white male rubber workers	Historical prospective mortality	White U.S. men	All causes	Excess deaths from specific cancers at specific work sites: gastrointestinal/processing, lung/tire curing, bladder/all workers, brain and lymphatic/tire building, leukemia/all workers
Monson and Fine (1978)	13,750 rubber workers; 1,359 deaths	Historical prospective mortality, morbidity	U.S. men, and within-plant comparisons	Cancer	Excess rates of cancer of gastrointestinal tract, lung, bladder, skin, brain, and hematopoietic tissues in specific jobs
Arp et al. (1983)	15 cases of lymphatic leukemia	Case-control	Other deceased employees, matched	Lymphocytic leukemia	Cases more likely than controls to have had exposure to benzene and other coal-tar-based solvents

NOTE: Smoking history was not considered in any of these studies.

cohort and the general male U.S. population, and also between cancer incidence in specific departments and incidence in all other departments combined. There appeared to be increased risks of various malignancies associated with certain work areas, notably cancers of the gastrointestinal tract, lung, bladder, skin, and brain, as well as lymphomas and leukemia. Interestingly, bladder cancer was not found to be in excess among workers presumably exposed to betanaphthylamine, and lung cancer did not occur with unusual frequency in work areas where operators had previously been found to exhibit respiratory morbidity. Lung cancer was found in excess among workers engaged in tire curing and molding and in deicing and fuel cell operations. No effort was made to take into account the role of smoking as a factor causing cancer in this worker cohort.

Studies of Workers Exposed to Aromatic Amines

Since the work of Rehn (1895), there has been increasing evidence that exposure to aromatic amines used in the dye-making industry is an important cause of bladder cancer. Case series reported in the United States (Evans 1937) and in the United Kingdom (Case et al. 1954) added evidence that naphthylamines and benzidine were the likely carcinogens accounting for the high incidence of bladder cancer in exposed chemical workers. Other studies of bladder cancer risk and exposure to aromatic amines have been reviewed recently (Clayson 1981; Johnson 1983). In addition, Melick and colleagues (1971) demonstrated that 4-aminobiphenyl is a bladder carcinogen, and there is concern that benzidine-derived dyes may also be carcinogenic (Johnson 1983).

Approximately 83,700 workers were employed in the manufacture of industrial organic chemicals in September 1984 (US DOL 1984). Some unknown fraction of these workers is exposed to aromatic amines. The National Institute for Occupational Safety and Health (NIOSH) (1979) estimated that 79,000 workers in various categories are exposed to benzidine and related chemicals. Since many of the aromatic amines are regulated as carcinogens and because new methods are available for synthesis of dyestuffs, exposure to aromatic amines has decreased (Johnson 1983). However, benzidine derivatives are still commonly used and have not been studied as extensively as other aromatic amines. Benzidine derivatives are known to be excreted as free benzidine in the urine of rhesus monkeys (Rinde and Troll 1975).

Mancuso and El-Attar (1967) conducted a retrospective cohort mortality study of 639 men who manufactured betanaphthylamine and benzidine. Fourteen deaths due to bladder cancer and one due to kidney cancer were observed, although less than one case was expected on the basis of the rates for Ohio residents. Six deaths due

to pancreatic cancer were also observed. Smoking histories were not obtained.

Zavon and colleagues (1973) identified a small cohort of workers involved in the manufacture of benzidine. These workers averaged 13 years of exposure to benzidine. Of the 25 workers, 13 developed bladder tumors and 4 developed kidney tumors. Smoking histories were not reported, so the possibility of interaction cannot be addressed.

A risk assessment of a cohort exposed to aromatic amines has recently been reported (Schulte et al. 1985). Thirteen confirmed cases of bladder cancer occurred in a cohort of 1,385 workers in a plant where betanaphthylamine and benzidine were manufactured and used intermittently from 1940 to 1972. Cases were identified from an ongoing mortality survey, from a bladder cancer screening clinic, and from a survey of local urologists. Incidence rates were calculated on the basis of person-years of exposure, and were compared with the Surveillance, Epidemiology, and End Results (SEER) program's incidence rates for the entire United States. Overall, bladder cancer incidence in the cohort was 3.9 times the incidence in the U.S. general population. The incidence rate increased dramatically with duration of employment; this increase was independent of age. Peak incidence occurred with people younger than most bladder cancer victims in the general population. Smoking histories were evaluated; no significant differences in smoking patterns were found between cases and controls.

The relationship between exposure to aromatic amines and bladder cancer has also been explored in case-control studies. These studies are reviewed later in this chapter.

Investigation of the carcinogenicity of betanaphthylamine and other aromatic amines has provided important insights into the nature of chemical carcinogenesis in general. Decades ago, it was realized that bladder carcinogenesis was a species-specific phenomenon: betanaphthylamine induced bladder tumors in dogs but not in rats or mice (Scott 1962). Carcinogenic potential apparently depends on the pathway of biotransformation of the amine compound and the efficiency of urinary excretion. This differs markedly in various species. Because the oxidation products formed are dependent on activities of various oxidizing enzymes (mainly hepatic), substances capable of modifying these enzyme activities (induction or inhibition) could influence the carcinogenicity of the aromatic amines. There is, therefore, a rational biochemical basis for xenobiotic interactions. It is now known that aromatic amines are capable of causing tumors in many organs and tissues of laboratory animals in addition to the urinary bladder. The distribution of cancers induced is again remarkably different among species (Clayson 1981). Finally, it is noteworthy that tobacco smoke contains measurable amounts of

carcinogenic aromatic amines (Wynder and Stellman 1981), and that betanaphthylamine and an oxidation product thereof have been identified in the urine of a cigarette smoker (Connor et al. 1983).

Studies of Workers Exposed to Pesticides

The Bureau of Labor Statistics (US DOL 1984) estimated that 36,700 workers were involved in the manufacture of agricultural chemicals in September 1984. This estimate does not, of course, include the much larger number of people exposed while using these chemicals, such as farmers and gardeners. These end-users exposed to pesticides could easily number over 1 million individuals.

A mortality survey of workers in pesticide application analyzed 311 deaths (Wang and MacMahon 1979a), comparing mortality rates for various causes with rates characteristic of the general U.S. population. Elevated SMRs were found for cancer of the lung, skin, and bladder, but only the elevated ratio for bladder (R 277) was statistically significant. The ratio did not correspond to the intensity of exposure, being much higher in those applications with minimal exposure. No attempt was made to assess the role of smoking as a factor accounting for the excess cancer mortalities. In a similar companion analysis of 113 deaths among workers engaged in the manufacture of chlordane and heptachlor (Wang and MacMahon 1979b), the investigators found a different pattern of mortality: there was no indication of excess cancer mortality at any study site. Smoking effects could not be taken into account. As is usual in occupational mortality surveys, overall mortality was substantially lower among the employed than in the general U.S. population (McMichael 1976).

Barthel (1981) surveyed 1,658 German male pesticide applicators in a retrospective cohort study, of whom 169 developed malignant tumors that resulted in death. These workers had applied a variety of fungicides, insecticides, and herbicides, usually in dust form. This report tabulated the specific pesticides that were used and included the period of time the cohort was likely to have been exposed to each specific pesticide. Compared with the male population of East Germany, this cohort had a 1.8-fold greater than expected mortality from bronchogenic carcinoma. Those individuals with the longest exposure to pesticide had the greatest risk of lung cancer mortality, e.g., a threefold increase in men exposed to pesticides for more than 19 years. Smoking was measured in a subsample of exposed workers and compared with age- and sex-matched controls selected at random from people receiving a chest x ray at a clinic for the general public. This source of controls can be criticized as being biased for people with chest disease and, therefore, smoking prevalence. Nonetheless, the pesticide-exposed workers and the controls had

similar smoking habits: 49.7 percent of the pesticide applicators were smokers versus 49.1 percent of the controls from the screening clinic. Lifetime tobacco exposures were also similar for the two groups.

Barthel speculated that the increased risk of lung cancer death could be partly attributed to arsenicals used prior to 1955 and possibly to asbestos present in the carrier substances (talcum, kaolin, and bentonite) used in pesticide dust formulations.

Mortality surveys were conducted (Ott et al. 1974) to detect excess cause-specific death rates among workers engaged in the manufacture of arsenical pesticides. Proportionate mortality ratios were calculated for the arsenic-exposed workers (173 decedents) and were compared with ratios derived from the mortality experience among approximately 1,800 nonexposed workers at the same company. Arsenic exposure was found to pose an average 3.5-fold increased risk of lung cancer, the magnitude depending on the estimated intensity (airborne arsenic concentrations) and duration of arsenic exposure. An elevated risk ratio was also found for lymphatic and hematopoietic malignancies (3.9), but this was based on just five cases (1.3 expected). There was no evident increase in risk for any other malignant disease. A cross-sectional review of smoking histories of the arsenic-exposed workers showed no differences from the employee population in general, and no relationship to arsenic dosage estimates.

A subsequent study examined causes of death among 1,393 persons (male and female) over several decades at a pesticide manufacturing plant in Baltimore, Maryland, where several hundred workers had been exposed to airborne arsenical compounds, mainly in the 1940s and 1950s (Mabuchi et al. 1979). Additional workers had been exposed to various other pesticides, including organochlorines and carbamates. Those who had left employment were traced. The mortality experience of the white population of the city of Baltimore was used for comparison, allowing the calculation of SMRs for the target population. As in the study by Ott and colleagues (1980), significantly and substantially elevated ratios were found for lung cancer among male workers exposed to arsenicals specifically. The ratios increased with the duration of employment in arsenical manufacture, suggesting a dose-response relationship. Two cases of anemia were identified, one pernicious and the other aplastic. No excess of lymphatic cancer was identified. Among workers involved in the manufacture of nonarsenical pesticides, the mortality pattern was essentially the same as that of the Baltimore city white population. Although the smoking habits of decedents were not determined, the authors offered cogent arguments in support of an occupational rather than a smoking causality: (1) SMRs for smoking-related causes of death other than lung cancer were not elevated in the arsenic-exposed group, and (2) the strong dose-response relation-

ship between arsenic exposure and lung cancer would not be expected to be paralleled by a concomitant increase in smoking risk, when no such relationship was found among workers engaged in the manufacture of nonarsenical pesticides.

Mortality among workers engaged in the manufacture of 2,4,5-T has been examined (Ott et al. 1980). These workers were presumably exposed to chlorodioxins. Mortality occurring among 204 workers from 1950 to 1971 was compared with that recently tabulated for all U.S. men. Of 11 deaths, only 1 was due to cancer; this was a respiratory tract malignancy in a 63-year-old retiree who had been exposed to the 2,4,5-T manufacturing process for 8 years and who smoked up to two packs of cigarettes daily.

As with the petrochemical worker mortality studies, the few studies of workers exposed to pesticides lack specific information from which to measure the contribution of smoking to the increased risk of cancer. Because cohorts of workers manufacturing pesticides are not large, it is unlikely that epidemiologic studies will be done to address specific questions regarding smoking and pesticide interactions.

Occupational Exposures and Smoking as Causal Factors in Specific Diseases

Several investigations have examined the role of occupational exposures as risk factors in the development of specific diseases. The case-control design has the disadvantage of being nonspecific and sometimes unreliable in identifying exposure that occurred in the workplace. The main advantage of this approach is the opportunity to collect information on other risk factors, specifically smoking, together with the greater statistical power that results from studying a larger number of cases than might occur in a specific industrial cohort. In this section, epidemiologic studies of various cancer types and chronic lung disease are reviewed.

All Cancers

Dubrow and Wegman (1984) examined the occupational characteristics of 16,629 cancer victims who died in Massachusetts between 1971 and 1973. They calculated the age-standardized mortality odds ratios for various types of cancer within 321 occupational categories, relying on death certificate indication of the "usual occupation" of the decedent, and attempted to adjust for social class. To limit the confounding effect of smoking on cancer incidence, they used adjustment factors based on published estimates of smoking frequency in major occupational groupings, together with lung cancer risk ratios for smokers and ex-smokers. The estimates of smoking frequency within occupational groups were based on a 1970 National

Health Interview Survey of 75,827 American men and women reported by Sterling and Weinkam (1976). The authors not only reported their own findings, but also compared their results with those from 11 other large-scale mortality surveys.

In this study a large number of occupations wherein death caused by particular forms of cancer appeared to be excessive was identified. Certain associations, such as lung cancer in shipyard workers, have been confirmed by other studies; the associations are plausible in terms of well-known exposures, especially exposure to asbestos. Significant excesses of bladder cancer were found among chemical workers and engineers, cosmetologists, leather workers, and garage mechanics, again generally in accord with the view that particular occupational exposures pose carcinogenic risks. High rates of certain cancers in schoolteachers, clergymen, administrators, judges, and lawyers are much more difficult to understand in environmental terms.

To the extent that the adjustment for smoking effects used in this analysis can be relied upon, the study would appear to show that certain occupations are, in fact, associated with excess risk of cancer, quite apart from the risk of smoking. It is not possible to estimate the relative magnitudes of the two risk factors, or the existence of interaction between them.

Data from the Third National Cancer Survey (TNCS) Interview Study of 7,518 incident cases were used to seek associations between various occupations and types of cancer (Williams et al. 1977). Data assembled on each case included a synopsis of lifetime employment, education, residential location, and use of tobacco and alcohol, as well as age, sex, race, and socioeconomic status. The large number of cases and the detailed information available made possible a number of adjustments and comparisons not possible in other studies. The main analytical strategy was to compare, serially, the proportions of specific main lifetime industries and occupations among patients with cancer at one site with proportions of patients having cancers at other sites combined as a control group (intercancer comparisons). The advantages and limitations of this approach were discussed by the authors. Even when smoking was controlled for statistically, people engaged in trucking were found to be at excess risk of lung cancer, a finding supported by the Massachusetts cancer mortality survey (Dubrow and Wegman 1984). Other transport, service, manufacturing, and construction workers were also at excess risk of lung cancer. As often happens, some associations were discovered that are difficult to understand mechanistically: excess leukemia and multiple myeloma in salespeople and malignant melanoma in schoolteachers, for example. The study does not present relative risk ratios for smoking within occupational categories from which the relative importance of the two factors might be assessed. As in the